Rapid Gastric Emptying of a Liquid Meal in Long-term Type 2 Diabetes Mellitus

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Both delayed and accelerated gastric emptying rate (GER) have been reported in patients with diabetes mellitus. Delayed GER has been attributed to autonomic neuropathy in established diabetes but rapid GER was demonstrated in early Type 2 diabetes. The aim of the study was to investigate rapid gastric emptying in a group of people with long-duration Type 2 diabetes. GER of a radiolabelled liquid meal was studied scintigraphically in 20 Type 2 patients with a mean (± SEM) duration of diabetes 13 (±1) years. The 50 % emptying time (t_{50}) for the liquid meal was shorter in diabetic patients (29.6 ± 2.1 min) than in controls (39.2 ± 1.9 min; $p<0.0005$). Accelerated emptying (t_{50} value below the shortest t_{50} of controls) was evidenced in 14/20 patients and delayed emptying (t_{50} value exceeding the upper t_{50} of controls) in none. Patients with accelerated GER were comparable for BMI, diabetes duration, HbA_{1c} and fasting glycaemia to those with normal GER. Rapid GER for liquids was found in the presence or absence of autonomic neuropathy. Seven of the patients with rapid emptying of the liquid meal were reassessed using a solid meal. Only one patient demonstrated rapid emptying of the solid meal, which was normal in 3 and delayed in 3 patients. In conclusion, accelerated GER can be found in long-term Type 2 diabetes but there is no concordance between GER of a liquid and a solid meal.

***Diabet. Med.* 15: 1022–1027 (1998)**

KEY WORDS **Type 2 diabetes mellitus; gastric emptying**

Received 8 August 1997; revised 3 July 1998; accepted 6 August 1998

Introduction

Disordered gastric emptying, a frequent finding in diabetic patients, may not only give rise to upper gastrointestinal symptoms but may also affect postprandial glucose excursions. While delayed gastric emptying may be as a late manifestation of Type 1 or Type 2 diabetes,[1–5] rapid gastric emptying has been hypothesized as characteristic for 'early' Type 2 diabetes.[5,6] Studies in patients with a long known duration of disease found delayed and not rapid gastric half-emptying time for a liquid meal.[3–5] These observations were concordant with delayed gastric emptying rates for a solid meal documented in patients with long-standing diabetes. Furthermore, no accelerated gastric emptying rate was recorded in Chinese Type 2 diabetic patients with long-term disease and upper gastrointestinal symptoms.[7] It should be noted that in most studies of gastric emptying of liquids in Type 2 diabetic patients, the emptying rate for a liquid meal was measured using a mixed liquid and solid meal. Such an approach may however hamper interpretation, as postprandial gastrointestinal motility is critically dependent on the meal composition and volume.[8–10] For example, at least in theory, the lack of normal adaptive relaxation in the proximal stomach of long-term diabetic patients[11,12] would lead to rapid rather than delayed gastric emptying of liquids. Therefore, using a scintigraphic technique, this study assessed the gastric emptying rate of 100 ml of a standardized liquid test meal in randomly selected Type 2 diabetic patients with known long-standing disease characterized in terms of glycaemic control, the existence of autonomic neuropathy, and lacking spontaneous upper gastrointestinal complaints. In a subgroup of patients, the findings on emptying of liquids were compared to the outcome of gastric emptying rate studied using a radiolabelled solid meal.

Patients and Methods

Subjects

Twenty patients with Type 2 diabetes (7 M/13 F; body weight 78 ± 2 kg) and 15 healthy volunteers without a family history of diabetes, were studied. Diabetic patients were recruited from the outpatient diabetic clinic on a first-come basis. Diagnosis of Type 2 diabetes was made according to the criteria of the National Diabetes Data

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 CCC 0742–3071/98/121022–06$17.50

Group.[13] The duration of known disease averaged 13 ± 1 years. Control subjects were selected to be comparable for gender mix (5 M/10 F) and body weight (71 ± 3 kg). The diabetic subjects were older (62 ± 2 years) than the non-diabetic volunteers (40 ± 3 years; $p < 0.0005$). All control subjects and patients were Caucasian, non-smokers, and none had a history of gastrointestinal (GI) surgery or evidence of GI disease. Fifteen diabetic patients were treated with insulin and sulphonylurea therapy and five were on sulphonylurea therapy alone. None was taking medication known to influence gastrointestinal motility. Written informed consent was obtained from all subjects and the study was approved by the local Ethics Committee which, in Belgium, includes evaluation by the Radiation Protection Board.

Assessment of Gastrointestinal Symptoms

Before measurement of gastric emptying, gastrointestinal symptoms were evaluated using a standard questionnaire proposed by Horowitz *et al*. 2–5 Anorexia, nausea, early satiety, bloating, upper abdominal discomfort or pain and vomiting were classified as 'gastric' symptoms and dysphagia, heartburn, and regurgitations as 'oesophageal'. Each symptom was scored as 0 = none, 1 = mild, 2 = moderate or 3 = severe, with a maximum possible score of 18 for the gastric and 9 for the oesophageal symptoms.

Assessment of Glycaemic Control, Autonomic Neuropathy, and Retinopathy

Glycated haemoglobin (HbA_{1c}) was determined in venous blood. The range in non-diabetic subjects in our laboratory is 4.3–5.7 %. Cardiovascular autonomic function tests were done as described by Ewing and Clark.[14,15] Parasympathetic function was evaluated by the heart rate variation (R–R interval) during deep breathing and during the Valsalva manoeuvre. Sympathetic function was assessed by measuring the systolic blood pressure response to standing. Each test was scored as 0 = normal, 1 = borderline or 2 = abnormal. Patients were classified as having autonomic neuropathy when at least two tests were abnormal. Retinopathy was diagnosed by fundoscopy and graded as background or proliferative.

Measurement of Gastric Emptying

Liquid Meal

All subjects were studied after an overnight fast of 10–16 hours. Insulin and sulphonylurea therapy was withheld the evening before the study. Gastric emptying was evaluated scintigraphically with a gamma camera using a 100 ml liquid test meal (= 100 kcal) that was labelled with 15 MBq of $_{99m}$technetium sulpur colloids ($_{99m}$Tc-SC) at 8.00 a.m. The test meal contained 15 % protein, 30 % lipid, and 55 carbohydrate (TONEXIS*, Clintec, Benclux NV, Brussels, Belgium). At 9.00 a.m., subjects were asked to ingest the test meal within 1 min in a sitting position. Immediately after intake, left anterior obliquus (LAO) registrations were performed with the subject in a supine position, taking a dynamic series of 60 images of 60 s duration over 60 min.[16] A region of interest (ROI) corresponding to the stomach was drawn to determine the gastric counts for each frame. Data were expressed as the percentage of radioactivity remaining in the stomach over time. The time before any emptying occurred (lag phase), the time for 50 % emptying (t_{50}) and for 25 % emptying (t_{75}) of the liquid meal were measured. The amount of kcal min^{-1} emptied was calculated from the t_{50} value. Abnormal gastric emptying was defined as a t_{50} value outside the t_{50} range of the non-diabetic controls.

Solid Meal

The GE study of a solid test meal was performed approximately 1 week after the GE study of a liquid test meal. The subjects were studied after an overnight fast of 10–16 h and withdrawal of hypoglycaemic therapy the evening before the study. The solid test meal consisted of an omelette labelled with 15 MBq of ^{99m}Tc-SC, 2 slices of bread, and 100 ml of drinking water (15 % protein, 55 % lipid and 25 % carbohydrate.[17] Subjects were positioned erect in front of the scintillation camera and anterior and posterior 60 s images were obtained every 15 min during 120 min (8 anterior and 8 posterior).

Glycaemia During Measurement of Gastric Emptying

Prior to the GE studies, an i.v. catheter was inserted into an antecubital vein. During GE of the liquid test meal, blood samples for measurement of glycaemia, using a hexokinase technique, were taken at −10 min before and at 10, 20, 30, 40, 50, and 60 min after intake of the liquid meal. During GE of a solid test meal, samples were taken before and at 60 and 120 min after ingestion of the meal.

Statistical Analysis

Results are expressed as the mean ± SEM. Data were analysed with the Mann–Whitney U test (unpaired data) and linear regression analysis. The significance of prevalence of results of gastric emptying was evaluated with the Fisher's exact test. A p value <0.05 was considered significant.

Results

Gastric Emptying of a Liquid Test Meal

Gastric Emptying Pattern

The gastric emptying pattern was characterized by an initial lag phase which lasted 7.9 ± 1.8 min in diabetic patients and 9.5 ± 1.6 min in healthy volunteers (p =

0.28). This lag period was followed by an emptying phase which was comparable in both groups till 10 min after the lag phase (Figure 1), the 25 % emptying time of the liquid meal (t_{75}) being similar for diabetic patients (13.7 ± 1.0 min.) and non-diabetic subjects (16.2 ± 1.6 min; $p = 0.11$). Between 20 and 40 min, the emptying phase became significantly faster in the diabetic group than in the control group (Figure 1, $p < 0.05$). The largest separation of gastric emptying rates between diabetic patients and controls occurred at 20 min after the lag phase (Figure 1, $p < 0.05$). The largest separation of gastric emptying rates between diabetic patients and controls occurred at 20 min after the lag phase (Figure 1, $p < 0.005$). The half-emptying time of the liquid meal (t_{50}) was significantly shorter for diabetic patients (29.6 ± 2.1 min) than for nondiabetic subjects (39.2 ± 1.9 min, $p < 0.0005$). The calculated average rate of calories emptied into the intestine by the diabetic patients was 1.8 ± 0.6 kcal min^{-}1, while the control subjects emptied at a rate of 1.3 ± 0.3 kcal min^{-1} ($p < 0.005$). In 14 out of 20 diabetic patients (70 %), the t_{50} was below the shortest t_{50} of healthy volunteers (Figure 2). None of the diabetic patients had delayed gastric emptying of the liquid meal. The lag phase in patients with rapid gastric emptying (6.6 ± 1.7 min) was not significantly different from the lag phase in patients with normal gastric emptying (11.2 ± 4.3 min, NS).

Glycaemia During the Test

Fasting glycaemia was significantly higher in diabetic patients (9.0 ± 1.6 mmol^{-1}) than in control subjects (3.9 ± 0.1 mmol^{-1}; $p < 0.0005$). There was no correlation between fasting glycaemia and liquid gastric emptying in diabetic patients.

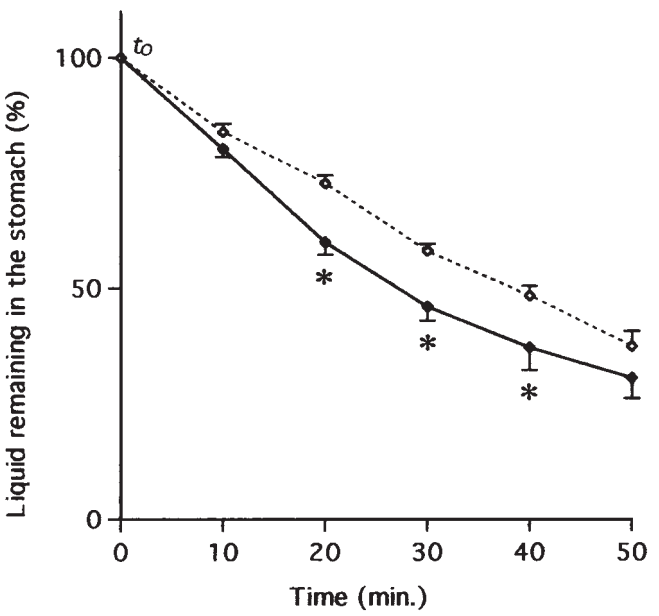

Figure 1. Per cent of liquid meal remaining in the stomach for diabetic patients (◆–◆ $n = 20$) and non-diabetic control subjects (◇–◇ $n = 15$). t_0 represents the end of the lag phase (*p<0.05)

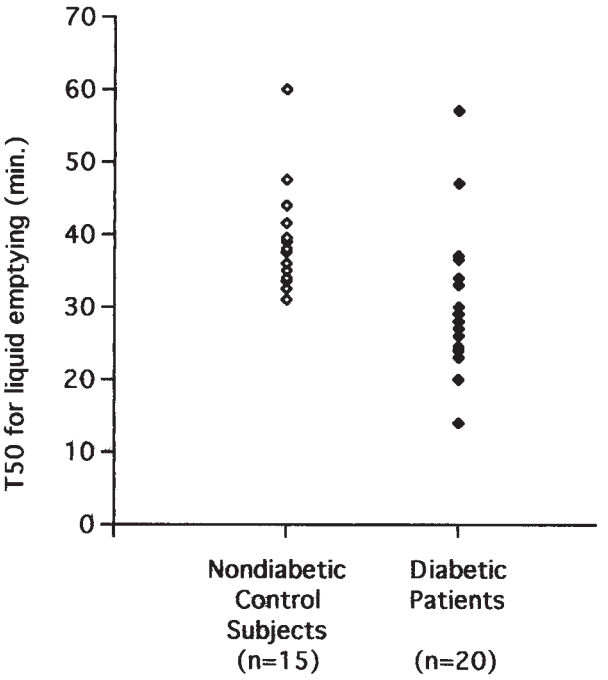

Figure 2. Individual results for liquid emptying expressed as the half-emptying time (t_{50}) in diabetic patients (◆ $n = 20$) and non-diabetic control subjects (◇ n = 15). Fourteen diabetic patients had rapid gastric emptying (p<0.0001)

Fasting glycemia was comparable in patients with rapid gastric emptying (9.3 ± 0.7 mmol l^{-1}; n = 14) and patients with normal t_{50} (8.3 ± 1.2 mmol l^{-1}; n = 6; NS). Changes in plasma glucose from baseline for these patients and non-diabetic subjects are shown in Figure 3. At 30 min after ingestion of the meal, the rise in plasma glucose from baseline was significantly higher only in diabetic patients with rapid emptying (Figure 3, $p < 0.03$) compared to healthy subjects. At 50 and 60 min, the increase in glycaemia was higher in all diabetic patients than in non-diabetic control subjects (Figure 3, $p < 0.0005$). No significant differences in glucose values or change of blood glucose values (Figure 3) were measured between diabetic rapid and normal emptiers.

Relationship Between Gastric Emptying Rate (GER) and Subject Characteristics

Gastric emptying of the liquid meal was not significantly related to age, body weight, gender, duration of known diabetes, HbA_{1c} in treatment modality or degree of metabolic control. The HbA_{1c} patients with rapid gastric emptying (8.1 ± 0.4 %) was lower than in the patients with normal gastric emptying (9.0 ± 0.5 %) but this did not reach significance ($p = 0.09$). Autonomic neuropathy was only encountered in two patients, one having a normal GER for liquids and one a rapid GER. Presence or absence of retinopathy was not correlated to GER.

Relationship Between Gastric Emptying and Gastrointestinal Symptoms (GIS)

Variable but predominantly mild gastrointestinal symptoms were reported by both diabetic patients and healthy controls. The median score for gastric symptoms was 0

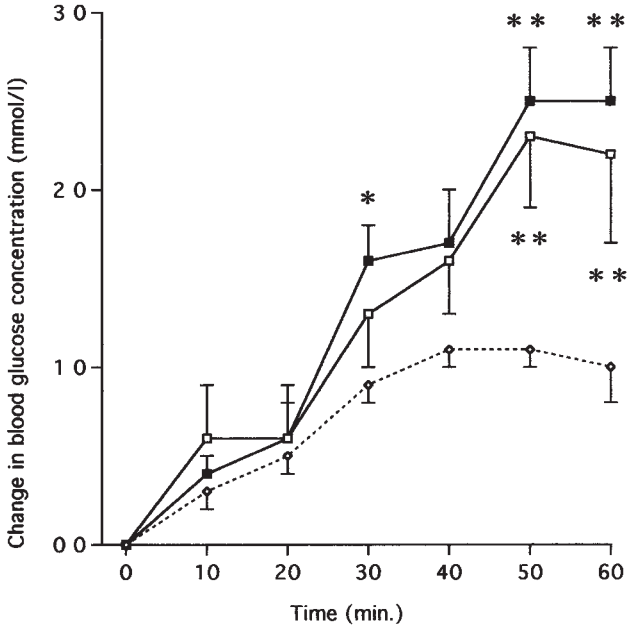

Figure 3. Changes from baseline of mean plasma glucose concentrations after ingestion of a liquid meal in diabetic patients with rapid (■–■ n = 14) and normal (□–□ n = 6) gastric emptying and in nondiabetic subjects (◇---◇ n = 15). Statistical differences between diabetic groups and non-diabetic control subjects: *p<0.05, **p<0.005

in all subjects (range 0–3 in diabetic patients and 0–1 in non-diabetic subjects), as was the median score for oesophageal symptoms (range 0–2 in diabetic patients and 0–1 in control subjects). The patient with the highest score and moderate complaints also showed the longest t_{50} value for liquids (57 min) although none of the tested subjects reported symptoms during the test. Early satiety and upper abdominal distention were scored in control subjects (3/15) and in diabetic patients with normal GER for liquids (2/6) but in none of the patients with accelerated GER (NS).

Gastric Emptying of a Solid Test Meal

Seven diabetic patients, who had rapid gastric emptying of the liquid test meal, consented to take a solid test meal. Ten control subjects, of similar gender mix and body weight, provided reference values. The control group was slightly younger (48.2 ± 6.3 years) than the diabetic group (63.8 ± 3.2 years; p = 0.07). Fasting glycaemia in diabetic patients before the GE study of the solid meal (10.3 ± 1 mmol l^{-1}) was not significantly different from the fasting glycaemia that was measured before the GE study of the liquid meal (9.4 ± 1 mmol $l^{\pm 1}$).

Individual t_{50} values are shown in Figure 4. The mean values for the groups were 69.4 ± 6.5 min (diabetic patients) and 58.8 ± 3.3 min (non-diabetic controls, p = 0.12). Only one patient with rapid emptying of the liquid meal also had rapid emptying of the solid meal. Furthermore, in 3/7 of the patients a delayed half-emptying time was measured. No correlation could be evidenced between the half-emptying time of a solid meal and the presence of GIS. Only one patient with delayed GER for solids had evidence of autonomic neuropathy.

Discussion

The main purpose of our study was to assess the prevalence of rapid gastric emptying of a nutrient liquid meal in a group of patients with long duration Type 2 diabetes mellitus. In this group, 70 % of the diabetic patients showed accelerated gastric emptying when compared to non-diabetic controls. The control group was younger than the diabetic group, but since ageing is associated with slower gastric emptying,[18] it is unlikely that this age difference is responsible for our results. The accelerated rate of emptying of liquids in asymptomatic Type 2 diabetic patients agrees with previous reports[5,6,9,19] but is at variance with Jones *et al.*[20] Phillips *et al.* documented rapid gastric emptying of a liquid meal in asymptomatic patients with recently diagnosed Type 2 diabetes[6] and claimed that a predisposition to rapid gastric emptying may play an important role in the pathogenesis of Type 2 diabetes.[6,19] Our patients had all had known diabetes for at least 5 years, which demonstrates that rapid emptying is not limited to the early years of disease. The fact that our patients have a longer duration of diabetes does not contest the hypothesis that

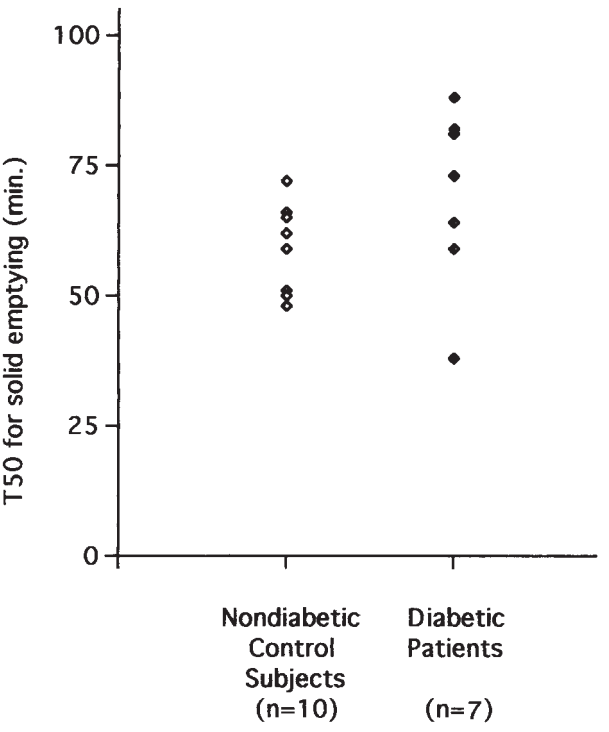

Figure 4. Individual results for solid emptying expressed as the half-emptying time (t_{50}) in diabetic patients with rapid emptying of the liquid meal (◆ n = 7) and in non-diabetic control subjects (◇ n = 10). Only one patient had rapid gastric emptying of the solid meal (p<0.0001). Four patients had delayed gastric emptying (p<0.05)

rapid emptying is a possible risk factor in the development of diabetes.[6,19] We hypothesize that rapid emptying may be present before the development of diabetes and can persist until vagal neuropathy disturbs the rapid emptying pattern.[21]

Rapid emptying for liquids has been described in Type 1 diabetes and may be a characteristic of diabetes *per se*.[22] The origin for this phenomenon remains unclear. In spontaneously diabetic Chinese hamsters with rapid gastric emptying, analyses of the vagus showed a significant decrease in the size of unmyelinated (afferent) fibres.[23] No arguments can be found in our study for a role of the degree of metabolic control or basal glycaemia in the occurrence of accelerated gastric emptying. Horowitz *et al*. demonstrated that hyperglycaemia in diabetes is associated with delayed gastric emptying[5,24] and healthy volunteers, even minor increments in basal glycaemia slow gastric emptying.[25] Some authors suggested that Type 2 diabetic patients lack modulation of gastric emptying by hyperglycaemia,[26,27] thereby explaining rapid gastric emptying patterns despite hyperglycaemia.

Our study underlines that accelerated gastric emptying can be encountered in the presence or absence of detectable autonomic neuropathy. It also stresses the discrepancies for gastric emptying between liquids and solids, as rapid gastric emptying for liquids could be associated with rapid, normal or delayed emptying for solids. This may be explained by the physiological mechanisms of gastric emptying. The proximal stomach plays an important role in the emptying of liquids,[11,12] while the emptying of solid food is predominantly controlled by the distal stomach. In diabetic patients, the tendency of the proximal part of the stomach to distend may be increased, which would explain why liquid food is pushed more rapidly through the pylorus into the duodenum. The distal stomach appears to have fewer antral contractions in diabetes in combination with increased isolated pyloric pressure waves,[1,28] causing retention of solid food in the distal stomach. Our findings are to some extent concordant with those of Frank *et al*. but at variance with other studies using a mixed liquid/solid meal to assess the GER.

We should take into account that the caloric content of the liquid meal used in our study was smaller than that of the solid meal. Since gastric emptying is dependent on the caloric content of a meal,[8,9,10] we would rather conclude that the discrepancies in the emptying of a caloric liquid meal and a solid meal is greater in Type 2 diabetic subjects than in normal controls. Furthermore an effect of posture cannot completely be ruled out, as the gastric emptying study for the liquid test meal was done in a semi-reclining position (30° from horizontal), while the gastric emptying study for the solid test meal was performed standing.

Although we found no significant correlation between the GER and the changes in glycaemia from baseline in our diabetic subjects, there was a trend to a steeper glycaemic rise in patients with rapid gastric emptying. When patients are compared to control subjects, gastric emptying rate did correlate with glycaemic changes from baseline. This is consistent with the findings of Phillips *et al*.[6] Gastrointestinal symptoms are known to correlate badly with GER in studies using mixed liquid/solid meals.[2–5,21,29] In our patients, such symptoms were only mild and not different between patients and controls, although early satiety and upper abdominal distension were completely absent in the patient group with accelerated gastric emptying.

We conclude that rapid gastric emptying of a liquid meal is not restricted to the early phase of Type 2 diabetes and that there are discrepancies between the gastric emptying of a liquid meal and that of a solid meal in patients with diabetes, which may explain some of the controversy in the literature.

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